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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/524,454	03/10/2000	Kristian Berg	697.013US1	5804

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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/524,454	Applicant(s) Berg et al.
	Examiner G.R. Ewoldt	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 21, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *21*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. The amendment, response, and declaration under 37 CFR 1.132 of Inventor Hogset, filed 11/21/02, have been entered.

2. Claims 1-11 are pending and being acted being acted upon.

3. In view of Applicant's amendment and response, filed 11/21/02, all previous rejections have been withdrawn.

4. The amendment filed 1/02/02 stands objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure for the reasons of record as set forth in Paper No. 16, mailed 6/18/02.

Applicant's arguments, filed 11/21/02, have been fully considered but they are not persuasive. Applicant asserts that one of skill in the art would see the amendment as the correction of a typographical error. Applicant is advised that an attorney's assertion as to what one of skill in the art would or would not see as a mere typographical error is insufficient to allow the change of actual data submitted in the specification. Applicant is advised that the submission of a proper declaration from the Inventor who performed the experiment in question, complete with the submission of the original results, e.g., a copy of the lab notebook in which the results were originally recorded, might comprise a convincing argument that would allow for the withdrawal of the objection and the entry of the change.

5. New corrected drawings must be filed with the changes incorporated therein. See the enclosed PTO Form 948. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of

Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections. Note that the filing of corrected drawings may no longer be held in abeyance until such time as claims are found allowable. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

6. The following are new grounds for rejection.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the abbreviation "$ArPcS_{2a}$" should properly be "$AlPcS_{2a}$".

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of inducing an *in vitro* T cell ^{51}chromium release response comprising culturing melanoma cells with a MART-1 peptide in 10ug/ml $AlPcS_{2a}$, followed by exposure to 1.35 mW/cm^2 of light generated by Philips TL 20W/09 bulb filtered through a Cinemoid 35 filter, followed by culture with primed MART-1-specific cytotoxic T cells,

does not reasonably provide enablement for:

a method of expressing a molecule on a cell comprising photochemical internalization wherein the molecule is sufficient to generate an immune response.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

The invention of the instant claims is drawn to a method of introducing enough antigenic peptide into a cell such that the cell is then capable of generating an immune response.

In Applicant's instant Remarks, filed 11/21/02, Applicant argues that the method of the instant claims has been demonstrated to function in the *in vitro* system of Example 2(set forth above). A declaration of Inventor Hogset, filed under 37 CFR 1.132, is also submitted in support of the invention. The declaration discloses an additional experiment as set forth in Example 2, including additional controls. In view of these Remarks and the declaration, the method disclosed in Example 2 has been found to be enabled. The disclosure is, however, still insufficient to support the method of the instant claims.

Applicant asserts that the it can be established, "as Dr. Hogset declares, that photochemical treatment results in MART-1 internalization, processing and presentation on the surface of the cells in a form such that immune effector T cells are able to recognize and eliminate those cells (paragraph 4 of the Declaration)." It remains the Examiner's position that no expressing, processing, or presentation has been demonstrated. The data merely show that the cells release ^{51}chromium which is

generally considered to be an indication of cell death. Applicant's presumptions regarding the process by which the ^{51}chromium is released cannot be considered to comprise a demonstration of the claimed process.

Regarding the generation or stimulation of an immune response, the single relevant example of the specification is insufficient support for the invention as broadly claimed. The term "immune response" encompasses both innate and adaptive responses, both *in vitro* and *in vivo*. Innate responses would include NK cell, as well as macrophage, basophil, neutrophil, and eosinophil responses. None of these types of responses are disclosed nor enabled by the specification. Adaptive responses would include both B cell and T cell response, both MHC Class 1 and Class II mediated. No B cell immune responses are disclosed. Even as regards a T cell response, the specification is silent regarding T helper responses or any *in vivo* responses. Accordingly, it is clear that the method of the instant claims cannot be enabled as broadly claimed by the single relevant example. The claimed method must then be considered highly unpredictable and requiring of undue experimentation.

In regards to the 1.132. declaration of Inventor Hogset, it is now disclosed that factors not disclosed in the specification are critical to the functionality of the claimed method. "Whether or not cell death results after photochemical treatment is principally dependent on two factors. Firstly the amount of toxic substances generated by the photosensitizing compounds on exposure to light and secondly, the presence and toxicity of molecules which are internalized during this process." Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation in view of these newly disclosed factors.

Regarding the photosensitizing compounds and exposure to light, while specific photosensitizing compounds are disclosed and claimed, no specific concentrations of said photosensitizing compounds (other than that used in Example 2) are claimed nor disclosed. Clearly, this parameter must be considered in that too much photosensitizing agent will induce cell death. Even more importantly, the declaration discloses that, whereas "the level of toxic substances which are generated may be controlled by the selection of the photosensitizer to be used, [and] the dose of that photosensitizer, but most crucially, the time of illumination which leads to increasing levels of the toxic

substances" [must be considered]. The declaration goes on to demonstrate that too little light will not induce internalization while too much light kills the cells. Again it is clear, particularly in regards to the light parameters, i.e., source (wavelength), intensity, and duration, that the specification provides insufficient support for the claimed method. Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation.

Finally, regarding the antigen to be internalized, the instant declaration states "the toxicity resulting from the molecules which are introduced may be readily controlled by selecting an appropriate toxic or non-toxic molecule for transfer, depending on the desired end use." The specification discloses however, that essentially any antigen can be used including "all manner" of pathogenic antigens, as well as peptides involved in diseases ranging from cancer to multiple sclerosis. The specification fails, however, to disclose how to "appropriately select" among the toxic and non-toxic molecules. Indeed, even the instant post-filing declaration fails to indicate how such a selection is to be made; it only indicates that said selection is essential, which once again demonstrates the lack of guidance in the specification.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples encompassing the breadth of the claimed invention, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

11. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of a method of "photochemical internalization as recited in the claims. The term is never actually defined in the specification, at page 4 however, it is disclosed that a "photodynamic effect" causing the introduction of molecules into the cytosol of a cell can be achieved employing a "photosensitizing agent" and "photoactivating light", and that "such a method [has been] termed "photochemical internalization"". Whereas a "photosensitizing agent" has been defined in the specification, "photoactivating light" has not. The only disclosure regarding a generic use of "light" is found at page 14, "the wavelength and intensity of the light may be selected according to the photosensitizing agent used. Suitable light sources are well known in the art." Said vague disclosure is insufficient description of a critical element of the claimed method. As the term would potentially encompass an essentially unlimited genus, i.e., all light, one of skill in the art would conclude that the specification fails to adequately describe the claimed method. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone numbers are 703-872-9306 (before final) and 703-872-9307 (after final).

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
February 5, 2003